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Mixed Donor Chimerism after Allogeneic Transplant in Patients with Wiskott-Aldrich Syndrome

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Background: Wiskott-Aldrich syndrome (WAS) is a rare X-linked disorder characterized by a triad of immunodeficiency, eczema and thrombocytopenia. This is as a result of mutation in the WASP gene that regulates actin polymerization in hematopoietic cells. Currently, stem cell transplant (SCT) is the most reliable curative treatment with excellent results for patients with HLA-matched family or unrelated donors. However, mixed donor chimerism even in the setting of full myeloablative regimens is still a significant problem since mixed chimerism affecting the myeloid compartment may result in persistent thrombocytopenia. Thus, identifying factors associated with mixed donor chimerism after SCT in WAS patients is extremely important.

Methods: We performed a retrospective chart review of eleven children who underwent allogeneic transplant for WAS to identify any factors (i.e. pretransplant health of the patients, degree of thrombocytopenia, conditioning regimen, infection, peri-transplant factors, TH2 flare) that may be associated with mixed donor chimerism.

Results: The median age at transplant was 16 months (range 3-39) and the donor was MRD in 4, MUD in 5 and MMUD in 2. All patients received bone marrow apart from one who received cord. The mean WAS score was 2.7 (range 1-5) and diagnosis was confirmed by genetic testing in all patients. All were conditioned with myeloablative regimens. Nine received busulfan, cyclophosphamide, Ara-C or fludarabine and campath while 2 patients got busulfan, cyclophosphamide and ATG. The median nucleated cell dose from the marrow was 5.3 x 109/kg (range 3 to 7.9). The median times to neutrophil and platelet engraftment were 22.5 (range 13-27) and 19 (range 17-31) days respectively. The overall survival by Kaplan Meier analysis is 91%, 95%CI: 51%-99% at 2 year post transplant. Only one patient developed grade IV aGvHD and died on Day +99. Five of eleven (45%) had mixed donor chimerism, (range: 7-50%). Of these 5 patients, 2 had normalization of the platelet count despite the mixed chimerism, 2 had full donor chimerism after receiving a second transplant with the same donor, and 1 remains transfusion dependent awaiting a 2nd transplant. No statistically significant difference was found between WAS scores, donor type, conditioning, stem cell source, age at transplant and mixed chimerism amongst the eleven patients.

Conclusions: Although the overall survival of our patient population was excellent, it does not reflect a uniform result in terms of engraftment. None of our peri-transplant parameters are predictive of mixed chimerism or engraftment outcome. More correlative work is needed to assess genotype-phenotype risk factors for engraftment as well as pre transplant immunologic and disease states to better assess the risk of mixed chimerism and guide interventions to promote engraftment.

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Haploidentical Stem Cell Transplantation As a Therapeutic Option in Children with Previous Cord Blood Transplantation and Graft Failure. Successful Results in a Mexican Hospital

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Currently, in our environment, 50% of patients requiring transplantation cannot undergo this procedure due to lack of a donor.

Twenty patients with different pathologies Eleven patients had graft acceptance (55%) with complete chimerism. Nine (45%) patients had primary graft failure. Of the patients subjected to HT as rescue in case of cord graft failure, it was noted that 100% of the patients are alive after 40 months of follow-up with a statistically significant difference ($p = 0.02$) compared with those subjected to HT as the primary choice. This case review describes HT as a therapeutic tool in children without an available donor. Our objective was to describe the clinical features, complications and deaths in a series of children undergoing HT in the Instituto Nacional de Pediatria (INP) since 2009.

We included all patients undergoing HT between July 2009 and November 2012 .

Conditioning was done with fludarabine (30 mg/m^2) for 2 days, anti-thymocyte globulin (1.5 mg/kg/day) for 3 days, nodal radiotherapy (7 Gy) and melphalan (70 mg/m^2/day) for 2 days. For graft vs. host disease (GVHD) prophylaxis, cyclosporine (6 mg/kg/day) was used from day -1.

The method of CD34+ selection was contemplated for patients with immunodeficiency and CD3+ depletion for patients with oncology/hematology diseases.

For bivariate analysis of qualitative variables, c^{2}and Student t test were performed. OS and DFS curves were performed with the Kaplan-Meier method using SPSS v.20.0. Differences between the rates of OS or DFS based on cell dose, age, gender, and paternal or maternal donor were made using the log-rank test; $p<0.05$ was considered significant.

The median of cells infused was as follows: CD34+ 10.9 x 10^6/kg (range: 2 to 32 x 10^6/kg), CD3+ 14.2 x 10^5/kg and CD19+ 3.4 x 10^5/kg.

11 patients achieved graft (55%) with complete chimerism. Nine patients (45%) had primary graft failure. Of the 11 patients with complete chimerism, two patients had graft loss due to relapse of ALL (at 4 and 12 months post-HT). In a third case there was loss of the graft due to cytomegalovirus (CMV) at 21 months post-HT. Of the patients subjected to HT as rescue in case of cord graft failure, it was noted that 100% of the patients were alive at 40 months of follow-up with a

statistically significant difference (p 0.02) compared with those subjected to HT as a first choice.
OS of 70% was reported at 40 months. OS and DFS for children with leukemia was 75% and 40%, respectively. For children with immunodeficiencies it was 65% and 15%, respectively, with a 40-month follow-up

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Factors Associated with CMV Disease in Pediatric Hematopoietic Stem Cell Transplantation

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Purpose: Cytomegalovirus (CMV) infection remains a significant source of morbidity in pediatric hematopoietic stem cell transplantation (HSCT). Current strategies for mitigating the effect of CMV on outcome include weekly measurement of CMV viral load in the blood through post-transplant day 100 and use of acyclovir prophylaxis in the peritransplant period in patients at risk for CMV infection (patients in which the HSCT donor or recipient had CMV IgG seropositivity indicative of latent infection). Risk factors predicting CMV infection in pediatric HSCT are not well understood, and factors affecting recurrence of CMV viremia following an initial episode have not been reported.
Methods: We performed a retrospective review of consecutive cases at our institution between 2011 and 2014 where the recipient was at risk for CMV infection. We calculated odds ratios (OR) and 95% confidence intervals (CI) of CMV reactivation as a function of HSCT characteristics. This study was approved by the Institutional Review Board of the Dana-Farber Cancer Institute.
Results: Out of a total of 91 at risk patients, 26 (29%) patients had CMV infection (defined as CMV viremia without target organ involvement) occurring at a median of 46 days following HSCT (range: 9-127). One patient died from biopsy-proven CMV pneumonitis. There was a trend towards recipients with underlying malignant conditions having increased risk of CMV infection compared to others (OR=2.3; 95% CI=0.9-6.0; p=0.08). There was a significantly increased risk of CMV infection in recipients of an umbilical cord blood compared to other sources (OR=9.45; 95% CI=1.8-50.6; p=0.009). Patients with acute graft-versus-host disease (aGVHD) had a significantly increased risk of CMV infection (OR=3.6; 95% CI=1.1-12.1; p=0.04). All patients with viremia received a 14-day course of antiviral and immunoglobulin therapy. Patients who failed to clear the virus completely from the blood at the end of 14 days of therapy had no increased risk of CMV recurrence (p=0.2). A total of 6/26 (23%) HSCT recipients experienced CMV recurrence, at a median of 33 days (range 9-74) following initial CMV clearance. In the subset of recipients who experienced a recurrence of CMV infection, there was a trend toward increased treatment-related mortality (TRM; OR=9.5; 95% CI = 0.7-132; p=0.09). However, among all recipients at risk, CMV viremia was not associated with increased TRM (p=0.7).
Conclusions: Pediatric patients seropositive for CMV who receive umbilical cord HSCTs have increased risk for CMV viremia in the post-HSCT period. CMV infection is associated with aGVHD. If treated with antivirals, recurrence of CMV can be prevented. Multiple episodes of CMV viremia may be associated with increased TRM. This study broadens understanding of CMV disease in pediatric HSCT, and is the first to analyze factors influencing recurrence of CMV infection.

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Late Onset Pulmonary Arterial Hypertension after Successful HSCT for Familial HLH

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Familial hemophagocytic lymphohistiocytosis (FHLH) has often been associated with high transplant-related mortality, typically from a variety of causes in the first 100 days post-HSCT. We report a case of occult pulmonary hypertension that developed 3 years after HSCT for FHLH. The patient was born at 28 weeks with a NICU course consisting of mild respiratory distress syndrome and unilateral grade II intraventricular hemorrhage. At 2.5 months of age, he developed fevers, splenomegaly, progressive pancytopenia, hypofibrinogenemia, hyperferritinemia, and bone marrow hemophagocytosis. He underwent initial treatment per HLH-2004 with good response. Genetic analysis revealed homozygous perforin 1 mutations. He proceeded with a 5/6 cord blood transplant with Bu/Cy/VP-16/ATG conditioning and GVHD prophylaxis with cyclosporine and steroids. He achieved successful engraftment with stable 100% donor chimerism.
Post-HSCT course was complicated by engraftment syndrome, steroid-responsive grade II skin and gut aGVHD, severe VOD treated with defibrotide, and prolonged intubation. He developed persistent renal failure, presumably due to chronic calcineurin toxicity. He underwent cadaveric renal transplant 10 months after HSCT. Clinical care over the next two years was all outpatient, but complicated by BK nephropathy.
Two months prior to his death, he presented with tachypnea and oxygen desaturation. CXR showed mild peribronchial opacities. Respiratory viral panel and echocardiogram were normal. His symptoms resolved quickly with albuterol. He was re-admitted a week later with similar symptoms. Repeat CXR and echocardiogram were unchanged. Due to persistent symptoms, he underwent bronchoscopy that was positive for *P. jirovecii* and was treated with high-dose Bactrim. One month after completing treatment, he presented to an outside ER with acute onset of dyspnea. He rapidly decompensated into PEA and was unable to be resuscitated. Autopsy showed intimal and medial thickening of his pulmonary arteries with marked luminal narrowing, consistent with pulmonary arterial hypertension (PAH).
There is one prior case report of two pediatric FHLH patients who died in the first year post-HSCT with PAH discovered on autopsy. Despite successful HSCT, there appears to be a pathologic link between FHLH and PAH, both early and late post-HSCT. PAH should be considered in any FHLH patient with respiratory symptoms and improved screening techniques are critically needed.